Genetics of Cutaneous Melanoma and Nevi

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To provide a state-of-the-art summary of currently available data about the genetics of cutaneous melanoma and nevi, we reviewed the pertinent literature and outlined the important findings on genetic analyses. Although the first English-language report of melanoma in 1820 contained a description of a melanoma-prone family, seminal studies by investigators at the National Cancer Institute and the University of Pennsylvania identified dysplastic nevi (DN) as an important melanoma precursor, suggested an autosomal dominant mode of inheritance for both melanoma and DN, and proposed that a melanoma-susceptibility gene (*CMM1*) was located on chromosome 1p36. This gene assignment has not yet been confirmed by independent investigators. A second melanoma gene, designated *CMM2*, has been mapped to chromosome 9p21. This gene assignment has been confirmed independently, and the cell cycle regulator $p16^{INK4a}$ has been proposed as a candidate gene; germline mutations in this gene have been identified in about half of melanoma-prone families. Germline mutations in the cyclin-dependent kinase gene *CDK4* (chromosome 12q14) have recently been described in two melanoma kindreds; this finding likely represents a third melanoma gene. A heritable determinant for total nevus number has been suggested, as has the presence of a major gene responsible for total nevus density in melanoma-prone families. An autosomal dominant mode of inheritance for DN has been proposed, and evidence suggests that DN may be a pleiotropic manifestation of the 1p36 familial melanoma gene. Several studies have shown a surprisingly high prevalence of DN on the skin of family members of probands with DN. In light of the extensive evidence documenting that persons with DN (both sporadic and familial) have an increased prospective risk for melanoma, these family studies suggest that relatives of persons with DN should be examined for DN and for melanoma. Overall, genetic determinants have a major role in the pathogenesis of normal nevi, DN, and melanoma. Elucidating the molecular basis of these genetic events promises to enhance melanoma risk reduction strategies and thereby reduce melanoma-associated mortality.

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AMS = atypical mole syndrome; CMM = cutaneous malignant melanoma; DN = dysplastic nevi; HLA = human leukocyte antigen; NCI = National Cancer Institute; NCI-Penn = National Cancer Institute and the University of Pennsylvania

The first English-language report that described the entity now known as "cutaneous malignant melanoma" (CMM) was, in fact, a familial occurrence of the disease.[1] These observations lay fallow for 132 years, until Cawley[2] made a similar observation in 1952. During the next 25 years, a series of anecdotal case reports appeared (for a review, see Greene and Fraumeni[3]) in which families with multiple cases of melanoma were described only as interesting curiosities; these publications prompted speculation that a hereditary variant of melanoma might exist. Formal genetic analysis is required to prove the existence of a mendelian basis for a specific disease. For melanoma, this work began in earnest in the late 1970s.

GENETICS OF MELANOMA

Fourteen melanoma-prone kindreds were studied by investigators at the National Cancer Institute (NCI) and the University of Pennsylvania (NCI-Penn). Distinguishing features of the hereditary melanoma syndrome in the NCI-Penn series included a younger-than-average age at diagnosis of melanoma, a striking predisposition toward multiple primary melanoma, and the presence of multiple, clinically atypical moles that were designated "dysplastic nevi" (DN).[4,5] In this cohort, almost all family members with CMM also had DN on their skin, and during prospective follow-up, new melanomas were diagnosed *only* in family members with DN. These investigators proposed that DN were both markers that identified those family members who were at increased

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risk of CMM and precursor lesions from which most newly diagnosed melanomas evolved. These findings were thought to be analogous to those previously made in families with colonic polyposis and colorectal cancer.

Segregation analysis suggested that when the disease trait was defined as either CMM or DN, an autosomal dominant model best fit the pattern in these families,[6] a finding that has been confirmed.[7] The NCI-Penn group found that the distribution of CMM and DN was so tightly linked that they seemed to represent pleiotropic manifestations of the same gene.[8] The Seventh Genetic Analysis Workshop reviewed primary data from previously reported melanoma-prone families and concluded that "the one finding that was consistent across all analyses was that dominant inheritance was strongly rejected."[9] Nonetheless, familial melanoma investigators have continued to base their analyses on the presumption that this trait is inherited in an autosomal dominant fashion.

This presumption is of vital importance because linkage analysis, the technique used to assign a putative genetic locus to a specific chromosomal site, requires that the genetic model and its characteristics be known. The first such analysis was performed by the NCI-Penn group without an a priori hypothesis about the site of the melanoma gene. This genomic search identified moderately strong evidence of linkage between CMM-DN and the Rh blood group locus, known to be on the short arm of chromosome 1.[6] Additional analysis led to the conclusion that a CMM-DN gene was located on chromosome 1p36.[10,11] The estimated penetrance of this gene, designated *CMM1*, was 82% by age 72 years.[12] As yet, no candidate gene from this chromosomal region has been identified. In fact, numerous investigators have failed to corroborate the gene assignment proposed by the NCI-Penn team.[13-16]

Both etiologic and diagnostic heterogeneity have been suggested as explanations for this discrepancy. Only two of eight Australian families with CMM studied included substantial numbers of subjects with DN.[15] In contrast, all the NCI families had DN. Clearly, some CMM-prone families do not have DN, and a different genetic locus may be operative in those kindreds. In addition, a Leiden cohort included some families with DN and little or no CMM.[13,17] No such families were in the NCI series. Furthermore, some of the Dutch families represent a genetic isolate.[18] Diagnostic inconsistencies are likely to contribute to the failure of other investigators to confirm the 1p36 gene assignment. For example, investigators in a study in Utah did not require cytologic atypia of melanocytes for the histologic diagnosis of DN.[14] As a result, the prevalence of so-called DN became so high that the genetic model did not fit. Thus, the 1p36 CMM-DN gene assignment remains viable despite the apparently contradictory findings of other investigators.

Recent observations, however, have shifted the focus of familial melanoma research to a second gene site, located on chromosome 9p. On the basis of studies performed on melanoma cell lines, which identified chromosome 9p as an area of frequent cytogenetic abnormality, the Utah group performed a linkage analysis in 11 CMM pedigrees. Cases of DN were not included in their analysis. Multipoint linkage analysis provided strong evidence for a dominant, partially penetrant melanoma susceptibility locus (designated *CMM2*) on 9p21.[19,20] The penetrance of this gene was estimated to be 53% by age 80 years, and gene carriers had higher nevus counts and nevus densities than did those who were not gene carriers. Among gene carriers, persons with melanoma had more exposure to sunlight than did those without melanoma; this relationship suggested a genetic-environmental interaction in melanoma susceptibility within these families.[21]

The 9p21 gene assignment for the *CMM2* locus has now been confirmed.[11,18,22-24] The NCI group found that some of their families showed linkage to 9p, whereas others had linkage to 1p.[11] They found statistically significant genetic heterogeneity in their cohort of families, supporting the existence of at least two melanoma-susceptibility genes, and also noted significant linkage to the 9p21 locus when cases of DN were included in the analysis. Dutch investigators suggested that evidence of linkage between *CMM2* and 9p21 became stronger when cases of DN were included in the model.[18,23] British investigators evaluated six families with multiple cases of melanoma and found evidence supporting linkage to 9p21 in three.[24] In one family, linkage to 9p21 clearly was not found (1p36 was not evaluated in that study); thus, further evidence was provided in support of the existence of more than one familial melanoma gene.

A candidate gene for *CMM2* has been identified on chromosome 9p21. This gene is designated $p16^{INK4a}$.[25] Its protein binds and inhibits cyclin-dependent kinases in vitro; therefore, it is thought to be an inhibitor of cell division. One could readily envision how mutations in such a protein might allow uninhibited or aberrant cell proliferation in a manner similar to that attributed to tumor-suppressor genes. The NCI group described germline p16 mutations in 33 of 36 patients with melanoma from 9 different families.[26] In addition, these mutations were not observed in patients with melanoma from families with linkage to the 1p36 melanoma locus, further support of the hypothesis that at least two melanoma-susceptibility genes exist. The mutant p16 proteins they identified were functionally impaired in their ability to inhibit the growth-promoting activity of cyclin/cyclin-dependent kinase complexes in vitro.[27] These observations provide a biochemical rationale for the hypothesis that carriers of certain $p16^{INK4a}$ mutations have an increased risk for melanoma. The Utah investigators, however, analyzed

p16^{INK4a} coding sequences in 13 families with linkage to 9p and in 38 additional melanoma-prone families.[28] In only two families were potential predisposing mutations found. Overall, germline mutations in this gene have been identified in about half of the melanoma-prone families studied.

Additional support for the candidacy of *p16*^{INK4a} has evolved from the controversy about whether cancers other than melanoma occur excessively in melanoma-prone families. Some investigators have reported no increase in the risk of nonmelanoma cancers,[12,29] whereas others have suggested that such excesses do occur, and pancreatic cancer has been of particular interest.[30,31] Goldstein and associates[32] compared the incidence of pancreatic cancer in 10 families with *p16*^{INK4a} mutations with that of 9 families with normal *p16*^{INK4a} function. A 22-fold increased risk of pancreatic cancer was found in the former (7 observed versus 0.32 expected), whereas no pancreatic cancer was observed in the latter families. A report of a single family prone to both melanoma and pancreatic cancer with a mutation in this gene supports this observation.[33] These data suggest that the occurrence of pancreatic cancer in melanoma-prone families may require a mutation in the *p16*^{INK4a} gene.

Could more than two melanoma-susceptibility genes exist? The rapidly unfolding reports of hereditary breast cancer and colon cancer provide ample precedent for such a possibility. A recent study evaluated 31 families with melanoma not linked to 9p21 for evidence of mutations in other genes that are part of the cyclin-dependent kinase/cyclin D cell growth regulatory pathway. Two unrelated families (6%) were found to have the same germline mutation in the cyclin-dependent kinase gene *CDK4* located on chromosome 12q14.[34] This finding likely represents a third melanoma gene (*CMM3*); it seems to function as a dominant oncogene, unlike most familial cancer-susceptibility genes which are tumor-suppressor genes. The mutated *CDK4* gene is resistant to the normal inhibition exerted by *p16*^{INK4a} and thus becomes an unregulated promoter of cell division.

Investigators have often speculated that a melanoma-susceptibility gene might be linked to the human leukocyte antigen (HLA) complex on chromosome 6p, although the largest reported series of families in which linkage between HLA and either melanoma or melanoma plus DN was studied yielded strong evidence *against* linkage.[35] Recently, the Queensland group readdressed this question with a linkage analysis of 16 Australian melanoma-prone families; the result was moderate, but not definitive, evidence in favor of linkage.[36] Whether a melanoma gene lies within or near the HLA gene complex remains to be determined. Cytogenetic studies have suggested that one or more genes on chromosomes 2, 3, 10, and 11 may also have a role in the development of melanoma,[37] but no definitive evidence has been reported. Additional melanoma-susceptibility genes will probably be identified as the molecular genetic tools necessary for such studies become increasingly sophisticated and powerful.

GENETICS OF NEVI

In comparison with melanoma, the genetic basis of nevi is less well understood. Relative to nevi in general, a study of counted nevi among 23 monozygotic and 22 dizygotic twin pairs revealed a strong correlation in the total number of nevi among the monozygotic twins ($r = 0.83$) but not among the dizygotic twins ($r = -0.24$).[38] A precise genetic model could not be specified because of the study design, but the data suggested a strong inherited basis for total nevus count.

The Utah group analyzed their families for total nevus number and total nevus density. The latter is a derived variable computed from mole size and number. Their analysis suggested the presence of a major gene that accounted for approximately 55% of the mole phenotype in the multiple-case families but no evidence of a major "mole gene" in the single-case families.[39] Total nevus density fit a mendelian pattern better than did total nevus number.

With reference to DN, the original analyses by the NCI-Penn team suggested an autosomal dominant mode of inheritance[6,10,11] and further indicated that CMM and DN might be pleiotropic manifestations of the same gene, *CMM1*.[8] As noted previously, some investigators have been unable to corroborate the importance of DN in their families with melanoma,[14-16] whereas others have confirmed the etiologic importance of DN in their kindreds.[18,40] Systematic evaluation of the reproducibility and accuracy of the histopathologic diagnosis of DN has generally supported the ability to apply established criteria successfully, although occasional exceptions are apparent. In the most rigorous of these studies, in which the presence of preselected criteria was used as a condition for the diagnosis of DN, the sensitivity, specificity, and positive and negative predictive values were 0.86, 0.91, 0.96, and 0.73, respectively.[41] Most likely, the failure to apply the well-described histologic criteria for DN rigorously, especially the requirement for readily recognizable melanocytic atypia, accounts for much of the controversy about the putative difficulties in rendering the pathologic diagnosis of DN.

Additional genetic and epidemiologic studies have used DN rather than melanoma as the starting point. A careful study of melanocytic nevi in a consecutive series of patients encountered in a large private dermatology practice[42] provided a cohort of patients unselected for family history of melanoma within which a nested case-control study could be performed. Twenty-five patients with DN were matched to 28 control subjects without DN, and all willing first-degree relatives of both cases and control subjects were examined

for DN.[43] DN were found among the relatives of 80% of the cases and of 4% of the control group. The relative risk of having DN was 7.2 if one or more relatives had DN. Three of the cases in the families with multiple cases of DN were found to have a first-degree relative with melanoma. This report suggested that relatives of unselected persons with DN are themselves likely to have DN and may also be at increased risk for melanoma. This same cohort was also subjected to a formal genetic analysis.[44] The estimated segregation ratio for a hypothetical DN gene was 0.52, consistent with an autosomal dominant mode of inheritance.

A skin examination was performed on 156 living family members of 31 probands initially classified as having sporadic, histologically verified DN.[45] These persons were classified as having "sporadic DN" because they *reported* no cases of either CMM or DN among their relatives. After the relatives were actually examined, however, 60% of the probands were found to have one or more relatives with DN. One relative was found to have malignant melanoma in situ at the time of the examination. Using data from a concurrent survey of 400 control subjects from the general population, Crijns and colleagues[45] estimated that relatives of probands with DN were 4 times more likely than unselected patients to have DN, and they reported the following conclusion: "screening of family members of patients with DNS [dysplastic nevus syndrome] without familial melanoma would appear to be useful...."

British investigators examined a series of 266 patients with melanoma and 305 control subjects for the presence of what they designated the "atypical mole syndrome" (AMS),[46] an alternative term for DN syndrome. On examination of 91 relatives of study subjects found to have AMS, 39% of the relatives also had AMS, in comparison with 15% of patients who had melanoma and 2% of the normal population.[40] Although a formal genetic analysis of nevus distribution in this cohort was not reported, the authors noted that the "mode of inheritance was consistent with a single autosomal dominant gene, with the AMS phenotype and melanoma as two possible expressions of the same gene," echoing the observations reported by Bale and coworkers.[8]

In summary, formal genetic analysis provides considerable support for the hypothesis that both the phenotype of common acquired nevi and the phenotype of DN are under genetic control. The mode of inheritance is not well understood for ordinary nevi, whereas an autosomal dominant model seems most plausible for DN. Substantial work remains to be done for comprehension of both nevus phenotypes. Meanwhile, relatives of patients with DN are clearly at increased risk of DN (and probably melanoma) themselves. Therefore, they constitute a subset of the general population among whom melanoma risk reduction and screening activities can be focused.[47]

THE DN CONTROVERSY

If DN are of such importance in the etiology of familial melanoma, why does a heated debate continue over whether these lesions exist at all and whether they can be diagnosed reliably?[48] Currently, two sets of data provide the most compelling support for the dysplastic nevus concept: (1) DN prevalence surveys performed in melanoma case-control studies and (2) prospective surveillance of various cohorts of patients with DN for the occurrence of melanoma.

With reference to the former, at least 11 case-control studies have been published in which both cases and control subjects were examined for the presence of DN or clinically atypical nevi.[46,49-60] In all these studies, the diagnosis of DN was established clinically. Thus, the debate over histologic criteria for diagnosis of DN becomes irrelevant to these results. With one exception,[51] DN emerged from these analyses as one of the most important risk factors for melanoma yet identified. On average, 34% of patients with melanoma had DN, in comparison with 11% of control subjects (Table 1). The summary relative risks for melanoma conferred by the presence of DN ranged from 1.0 to 16.7 (median, 5.2), and several studies documented an increasing risk of melanoma as the number of DN or atypical nevi increased (Table 1). These studies provide strong evidence that DN, variably but clinically defined, are a potent risk factor for melanoma.

The best evidence regarding the validity of the DN concept derives from observations that document the excess risk of melanoma in various cohorts of patients with DN that have been monitored prospectively for new melanomas. Seven prospective cohorts of patients with familial DN have been reported (Table 2).[4,12,61-66] Noteworthy observations in these studies include the almost exclusive occurrence of new melanomas in family members with DN, the remarkably increased relative risks for melanoma, the striking number of melanomas diagnosed at an in situ stage (35% of all prospectively diagnosed melanomas), and the relatively thin (that is, biologically "early") average melanoma thickness at diagnosis. These findings clearly demonstrate that the presence of DN identifies those specific family members who are at increased risk for melanoma and imply that the prognosis for those family members whose melanomas are diagnosed as a consequence of active surveillance should be excellent.

Finally, prospective studies have now demonstrated that patients with DN without an obvious family history of melanoma and patients with DN selected without regard to their family history have an increased risk for occurrence of melanoma (Table 3). The findings parallel those seen in patients with familial DN, except that the relative risks for melanoma are lower. Thus, DN *do* help identify persons at increased risk for melanoma, even outside the context of melanoma-

Table 1.—**Prevalence of Dysplastic Nevi in Published Melanoma Case-Control Studies***

Reference	Cases (no.)	Control subjects (no.)	Variable	Dysplastic nevi (%)		Dysplastic nevi (no.)	Relative risk
				Cases	Control subjects		
Nordlund et al[50]	296	145	Atypical nevi	34	7	...	7.4
Cristofolini et al[51]	103	205	Dysplastic nevi	6	4	...	1.4
Swerdlow et al[53]	180	197	Large nevi	31	11	...	3.9
						0	1.0
						1-4	5.2
						5+	5.7
Roush et al[60]	246	134	Dysplastic nevi	34	7	...	7.6
Kelly et al[54]	121	139	Dysplastic nevi	55	17	...	6.0
						0	1.0
						1-5	3.8
						6+	6.3
Grob et al[55]	207	295	Clinically atypical nevi	34	21	...	1.9
Halpern et al[56]	105	181	Dysplastic nevi	39	7	...	6.8
Stierner et al[57]	121	310	Dysplastic nevi	56	19	...	5.4
Newton et al[46]	266	305	Atypical mole syndrome	15	2	...	7.5
Garbe et al[58]	496	476	Clinically atypical nevi	37	17	...	2.8
						0	1.0
						1-4	1.6
						5+	6.1
Holly et al[59]	452	930	Large nevi	NA	NA	0	1.0
						1-3	4.5
						4-7	6.1
						8+	16.7

*NA = not available.

prone families.[71] Furthermore, recognition of this class of atypical melanocytic lesions has allowed the formulation of a rational, biologically plausible model of melanocytic tumor progression.[72]

Why, then, would the panel members of the National Institutes of Health Consensus Conference on Diagnosis and Treatment of Early Melanoma recommend discontinuing use of the term "dysplastic nevus" and substituting instead "nevus with architectural disorder" with a statement about the presence and degree of melanocytic atypia?[73] This decision is puzzling because most of the foregoing data were available to the Consensus Panel. Of note, the expert dermatopathology working group that was convened in support of the Consensus Conference to review diagnostic crite-

Table 2.—**Prospective Melanoma Diagnosis Associated With Familial Dysplastic Nevi***

Reference	Families (no.)	Patients (no.)	Prospective CMM	Mean thickness (mm)	Clark level		DNS (%)	CMM relative risk†
					I	II		
Greene et al[4]	14	(Series updated by Tucker et al,[12] see below)						
Vasen et al [61]	9	NA	20	0.54	7	8	NA	NA
Rigel et al[62]	NA	105	11	0.43	7	4	100	167
Masri et al[63]	264	555	28	0.52	5	12	NA	NA
MacKie et al[64]	6	7	8	0.69	2	6	100	444
Tucker et al[12]	23	470	77	NA	30	47	100	DN, 85; DN-CMM, 229
Carey et al[65]	311	710	40	0.56	77%		100	DN, 116; DN-CMM, 964
Tiersten et al[66]	NA	105	3	NA	NA		100	53

*CMM = cutaneous malignant melanoma; DN = dysplastic nevus; DN-CMM = patients with dysplastic nevus who had melanoma diagnosed before entry into study; DNS = dysplastic nevus syndrome; NA = not available.
†Computed with use of only invasive melanomas.

Table 3.—**Prospective Melanoma Diagnosis in Unselected Patients With Dysplastic Nevus***

Reference	Prior CMM	Subjects (no.)	Prospective CMM	Mean thickness (mm)	Clark level I	Clark level II	CMM relative risk†
Rigel et al[62]	No	281	4	0.88	3	1	16
	Yes	66	3	0.26	2	1	36
Tiersten et al[66]	No	157	4	NA	NA		53
	Yes	95	4	NA	NA		74
Halpern et al[67]	No	89	2	0.52	0	2	154/100,000 per year
MacKie et al[64]	No	85	9	0.96	4	5	93
	Yes	24	3	0.78	1	4‡	91
Kang et al[68]	No	84	2	0.75	NA§	2	NA
Marghoob et al[69]	No	124	10	NA	NA		63
	Yes	163	...	NA	NA		90
Schneider et al[70]	No	267	5	NA	NA		47

*CMM = cutaneous malignant melanoma; NA = not available.
†Computed with use of only invasive melanomas.
‡Two patients each had two primary melanomas.
§In this study, 25% of patients had removal of at least one nevus with "severe nuclear atypia." Some of these were likely melanoma in situ lesions.

ria for various melanocytic lesions did *not* object to use of the term "dysplastic nevus." Rather, their conclusion was as follows: "The diagnosis of dysplastic nevus necessitates fulfillment of two criteria: (a) architectural disorder, and (b) easily identifiable melanocytic atypia. In the case of nevi exhibiting the first but not the second of these criteria, it was agreed to employ the term nevus with architectural disorder."[74] It seems likely that if workers in this field carefully applied the published and validated clinical and histologic criteria, most of the confusion and controversy over DN would be eliminated. Difficult-to-classify melanocytic lesions would occasionally be encountered at the extreme ends of the spectrum of melanocytic proliferation—that is, between ordinary nevi and lesions with mild melanocytic atypia at the one end and between severely DN and melanoma in situ at the other. Most dysplastic melanocytic lesions—those in the center of this spectrum—are readily recognizable.

In a recent editorial,[75] the pros and cons of this vexing controversy were acknowledged:

> But no amount of academic massage can eliminate the dysplastic nevus....Melanocytic dysplasia is here to stay, and its definition will ultimately emphasize a spectrum of cellular atypia. Our dilemma is that although histologic description of melanocytic dysplasia is a troubling and difficult area, we cannot simply wash our hands of it because the concept is too important to abandon; these lesions are potentially important in the early detection and prevention of melanoma.

CONCLUSION

As one surveys the progress that has been made from the brilliant clinical observation reported by William Norris in 1820 to the extraordinary molecular genetic revelations of the 1990s, it is clear that the study of familial melanoma has come a long way. We now know that at least three genes are involved in familial melanoma, and the definition of the molecular pathophysiologic aspects of two of them is imminent. We also know that heredity is an important determinant of nevus phenotype and that one particular melanocytic lesion, the dysplastic nevus, is a potent determinant of melanoma risk, both familial and nonfamilial. Thus, melanoma screening and risk reduction activities can be focused on people with familial CMM and with DN, with the data-based expectation that melanoma-associated morbidity and mortality are likely to decline as a result.

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